

UTILIZING GENETIC AND LIVE CELL MICROSCOPY TOOLS TO STUDY α -SYNUCLEIN MISFOLDING IN TWO YEASTS

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Correct protein folding and proper degradation of misfolded proteins are two vital processes that help maintain cell function and viability. Disruption in these events can lead to accumulation of misfolded and aggregation-prone proteins. Accumulation of aggregated proteins is characteristic of many neurodegenerative disorders, including Parkinson's Disease (PD). Sporadic and familial cases of PD are marked by death of dopaminergic neurons and aggregation of the protein α -synuclein into large inclusions known as Lewy Bodies. PD is a good model for studying protein misfolding because familial PD is linked to three genes involved in the protein degradation pathway. Thus far, α -synuclein misfolding has been modeled in flies, bacteria, and mice, but not in yeasts. Yeasts (*S. cerevisiae* and *S. pombe*) have emerged as powerful eukaryotic model organisms for studying the cell biology of protein folding and degradation. Given the powerful ability to genetically manipulate and biochemically examine both organisms, our lab has chosen to model α -synuclein misfolding comparatively in both yeasts. Our lab has already expressed wild-type and disease-linked mutant α -synuclein in both *S. cerevisiae* and *S. pombe*. In *S. cerevisiae*, some α -synuclein mutants are resistant to solubilization and appear more stable than the wild-type form. To strengthen both models and to further dissect misfolding mechanisms, we are currently using genetic approaches and live cell microscopy tools. In both forms of yeast, we have created C-terminal and N-terminal green fluorescence protein tagged versions of α -synuclein to visualize misfolding within living cells. Secondly, we are genetically assessing α -synuclein stability, solubility, and fluorescence in *S. cerevisiae* strains compromised for protein degradation as a result of expressing mutant proteasomal subunits. Studies in these two model yeasts may shed insight on the relationship between protein misfolding and degradation linked to PD.